# Effects of Antidepressant Treatments on Corticotropin-Releasing Hormone mRNA Expression in Rat Brain

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Antidepressant drugs exert many neurochemical effects on serotonin, adrenergic, dopaminergic, and GABAergic systems in rat brain. Many of these effects occur acutely and do not correspond with the prolonged time period required to achieve therapeutic efficacy of antidepressants in patients with major depression. We proposed that the delayed therapeutic effects of antidepressant treatment are due to secondary actions on corticotropin-releasing hormone (CRH) in the paraventricular nucleus (PVN) of the hypothalamus. *In situ* hybridization histochemistry was used to identify CNS systems which are selectively altered by long-term administration of antidepressant agents. We focused on two CNS systems which are thought to be dysregulated in classic melancholic depression, namely the hypothalamic-pituitary-adrenal (HPA) and the locus coeruleus-norepinephrine systems.

In the first study, the prototypic tricyclic antidepressant imipramine (5 mg/kg, i.p.) was administered daily for 2 (short-term)or 8 weeks (long-term). Long-term imipramine treatment decreased CRH mRNA levels in the PVN and decreased tyrosine hydroxylase (TH) mRNA levels in the locus coeruleus (LC). These changes were associated with an increase in mRNA levels of the hippocampal mineralocorticoid receptor (MR, Type I), thought to play an important role in mediating the negative feedback effects of low levels of steroids on the HPA axis. Imipramine also decreased pro-opiomelanocortin (POMC) mRNA levels in the anterior pituitary and plasma ACTH levels, in accordance with a functional down-regulation of the hypothalamic-pituitary axis. With the exception of a small decrease in TH mRNA in the LC after 2 wk of imipramine administration, none of these mRNA changes occurred after short-term administration. In the light of data that major depression is associated with an activation of brain CRH and LC-NE systems, the time-dependent effect of long-term imipramine administration on decreasing the mRNA expression of CRH in the PVN and TH in the LC may be relevant to the therapeutic efficacy of this agent in the treatment of classic melancholic depression.

To examine the generality of these findings, we examined the effects of 3 different classes of activating antidepressant drugs which tend to be preferentially effective in treating atypical depressions associated with lethargy, hypersomnia, and hyperphagia. The selective 5-HT reuptake inhibitor fluoxetine, the selective $\alpha_2$-adrenergic receptor antagonist idazoxan, and the nonspecific monoamine oxidase A and B inhibitor phenelzine were administered daily (5 mg/kg, i.p.) for 2 or 8 weeks. All 3 drugs increased TH mRNA levels in the LC after 2 or 8 weeks of treatment. The 3 drugs decreased CRH mRNA levels in the PVN only after 8 weeks of drug administration. No consistent changes in steroid hormone receptor mRNA levels were seen in the hippocampus with the 3 drugs.

In summary, the prototypic antidepressant imipramine shares with fluoxetine, idazoxan, and phenelzine the property of decreasing the expression of CRH mRNA in the PVN after chronic administration. In contrast, imipramine, which is preferentially effective in treating melancholic depression, decreases TH mRNA levels in the LC, whereas the other 3 drugs elevate TH. The preferential efficacy of activating antidepressants in atypical depression may reflect a capacity to increase the expression of TH mRNA in the LC, an effect that could theoretically be utilized in the screening of pharmacologic agents for the treatment of this disorder. The reduction in the mRNA expression of CRH in the PVN may be one common element relevant to the therapeutic efficacy of antidepressant drugs in the treatment of various forms of major depression.